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Prosthetic heart valve obstruction: thrombolysis or surgical treatment?

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Abstract

Prosthetic valve thrombosis is a potentially life-threatening complication associated with high morbidity and mortality. Transthorasic and transoesophageal echocardiography play an important role to the diagnosis and provides incremental information about the optimal treatment strategy, while fluoroscopy and cardiac computed tomography may be of added value. Guidelines differ on whether surgical treatment or fibrinolysis should be the treatment of choice for the management of left-sided prosthetic valve thrombosis and these uncertainties underline the need for further prospective randomized controlled trials. Thrombus size, New York Heart Association functional class of the patient, the possible contraindications, the availability of each therapeutic option and the clinician's experience are important determinants for the management of prosthetic valve thrombosis.

Keywords

Pannus, prosthetic valve, thrombolysis, thrombosis

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Introduction

Prosthetic valve obstruction (PVO) is an infrequent but serious complication in patients with prosthetic heart valve and is associated with significant morbidity and mortality.[1,2] It is frequently related to thrombus formation, secondary to pannus formation, and rarely to vegetation.[3] Prosthetic valve thrombosis (PVT) has an incidence between 0.1% to almost 6% per patient-year of left-sided valves and up to 20% of tricuspid valves.[4] PVT depends on valve type, anticoagulation status, valve position, the presence of atrial fibrillation, and/or ventricular dysfunction. The most common cause is an inadequate anticoagulant therapy.

Pathophysiology

Prosthetic valve thrombosis

PVT is mostly a complication of mechanical valves, while pannus formation is common to both bioprostheses and mechanical valves.[5] Reasons for the increased thrombogenicity of mechanical valves are the interaction of blood constituents such as platelet and blood cells first with injured endocardium immediately after the surgery, secondly with the surface of the mechanical valve that has thrombogenic properties leading to both platelet deposition and activation of factor XII, and thirdly with structural and metabolic changes due to irregular flow patterns arising around the prosthetic devices.[6,7] Thrombus formation usually begins at the hinges of mechanical valves.[8] Increased incidence of thrombotic events up to 10% have been reported in the first 3−6 months after implantation of the valve mainly in the mitral position. This can be explained by the hypercoagulable state after surgery and the contact of bloodstream with the nonendothelialized thrombogenic surfaces particularly on suture sites and prosthesis material.[9] Bioprosthetic valves have a considerably less frequency of thrombosis, approximately 0.03% per year mainly seen in the first months following surgery while the sewing ring becomes endothelialized.[10,11]

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Pannus ingrowth

Pannus formation is fibroconnective tissue ingrowth from the sewing ring and typically occurs after many years of valve implantation. Its formation is unaffected by routine anticoagulation.[12] It is generally considered as a bioreaction to the prosthesis and occurs more often on aortic mechanical prostheses as well as around the prosthetic ring after mitral repair. A thrombus layer can be formed secondarily on a pannus.

Clinical presentation

Obstructive PVT (OPVT) can present along a wide spectrum that includes systemic embolism, the insidious onset of fatigue, and shortness of breath developing over weeks to acute haemodynamic deterioration and death.[2] Patients with nonobstructive thrombi (NOPVT) present minimal clinical symptoms and they are stable but they constitute a group of high embolic potential.[13] Distinction between thrombus and pannus formation based on clinical grounds may be difficult. Generally, patients with thrombus formation have shorter duration of symptoms and more often inadequate anticoagulation.[12] In the clinical suspicion of endocarditis, blood cultures should be performed to exclude this entity. Although physical examination is frequently insufficient, it can reveal decreased prosthetic valve sounds, a new murmur, or change in a previously detected murmur. The diagnosis of PVO is established by transthoracic echocardiography (TTE), fluoroscopy and, above all, transoesophageal echocardiography (TEE).

Diagnosis

Transthoracic echocardiography

The examination of a patient with prosthetic cardiac valve by TTE is an essential part of diagnostic assessment.[14,15] TTE examination can be limited because the prosthesis produces a certain degree of acoustic shadowing caused by the highly reflective material itself and characteristic reverberations which need to be distinguished from vegetation or a thrombus. Doppler echocardiography is the most accurate method for detecting and quantifying the degree of transvalvar gradient increase and is useful in the follow up of patients during thrombolysis.

For mitral prostheses, the degree of stenosis is assessed by measuring early peak velocity, mean gradient, mitral Doppler velocity index (DVI), pressure half-time, and effective orifice area (EOA) by continuity equation, as well as the tricuspid regurgitation velocity in order to estimate pulmonary artery pressure. For aortic prostheses, peak and mean gradients and aortic DVI and EOA are generally measured.[14,15] It is important to remember that increased flow velocity itself does not always reflect prosthetic obstruction. It can also be caused by high output state, the presence of severe prosthetic regurgitation, patient−prosthesis mismatch, and the pressure recovery phenomenon. Hence, if clinical suspicion remains, the investigation should be completed with TEE, fluoroscopy, and/or computed tomography, which allow exact analysis of the discs' motion.

Transoesophageal echocardiography

TEE can help to assess thrombus size and location by its high-resolution imaging and can aid in treatment decisions, such as thrombolysis, anticoagulation, and surgery.[15] TEE along with clinical parameters can usually differentiate thrombus from pannus formation and vegetation. A pannus tends to be small and more echodense than a thrombus and in 30% of cases may not be distinctly visualized (Figure 1A). A pannus can extend onto the bioprosthetic cusps, leading to stiffening, or may interfere with valve closure and opening by impinging on the hinge mechanism of a mechanical valve (Figure 1B).[12] A thrombus is a mass with soft ultrasound density similar to that of the myocardium and usually greater total mass length compared to a pannus (Figure 2).

Mitral and tricuspid prostheses can be excellently visualized by TEE because of their *en face* position in relation to the imaging plane. TEE plays less of a role in assessing mechanical aortic valves, while bioprostheses or homografts have no problem in imaging with TEE. It has been reported that occluding disc angles of mitral prostheses could be ascertained in 100% by TEE. However, fluoroscopy and computed tomography are more helpful to detect disc mobility on both mitral and aortic position. However, TEE is advantageous in assessing patients who underwent replacement of the ascending aorta and aortic valve and providing incremental information about the whole thoracic aorta including the graft.[16]

Identification of a nonobstructive small thrombus can often be difficult and should differentiate from filamentous strands of varying length which have been seen attached to prosthetic valves.[1] They have been observed as early as 2 hours after valve replacement, suggesting that they are composed of fibrin. The role of these strands in cardioembolic events remains unclear.[17]

The thrombus size visualized by TEE is important in deciding on the optimal treatment strategy. When thrombolysis is contemplated, then TEE and Doppler echocardiography are the preferred modalities to assess serially the haemodynamic success of fibrinolysis. It has been reported that in left-sided obstructive PVT, a thrombus area <0.85 cm^2 confers a lower risk for embolism or death associated with thrombolysis.[18] The coexistence of panni on valves may be another explanation for abnormal flow patterns and the predilection to recurrent PVT.

Other reasons of obstruction could be mitral chordal remnants, which can interfere with proper disc/leaflet

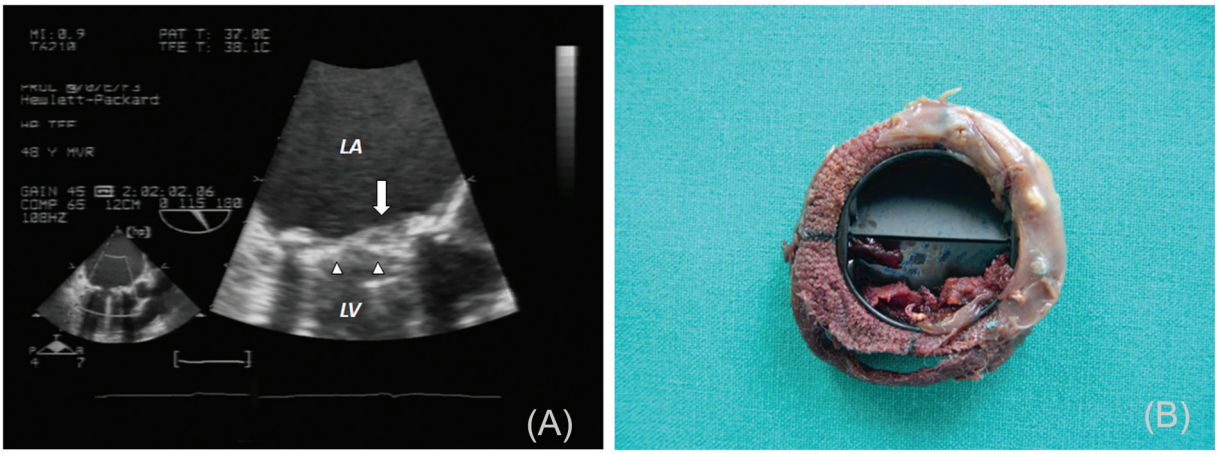

Figure 1. (A) A 40-year-old woman with a bileaflet mechanical mitral prosthesis which was implanted 3 years ago, presented with progressive dyspnoea during the last 6 months. Prosthetic mitral valve mean gradient was increased and transoesophageal echocardiogram showed an echodense mass on the prosthesis consistent with pannus. (B) Surgical specimen, the pannus on the atrial surface of the mitral prosthesis
Arrow, pannus; arrowheads, the two hemidiscs. LA, left atrium; LV, left ventricle.

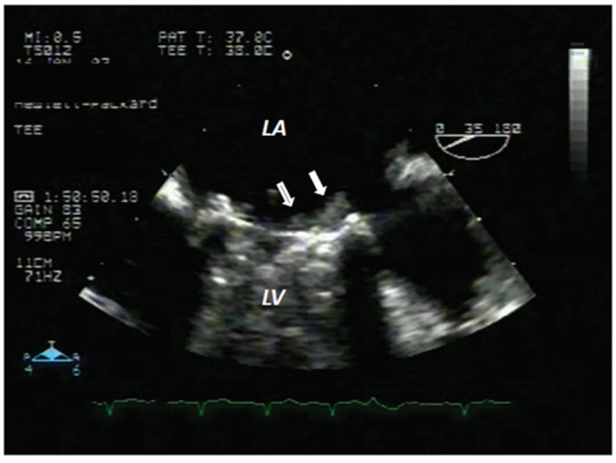

Figure 2. A 35-year-old woman presented with acute pulmonary oedema and was operated urgently. Transoesophageal echocardiogram showing a large obstructive thrombus (arrows) visualized as a soft mass on the atrial surface of a single tilting disc mitral prosthesis.
LA, left atrium; LV, left ventricle.

motion. If sutures are not cut short enough or become unraveled, they can caught in the valve housing and cause sticking. Left ventricular outflow tract obstruction can occur with retention of the anterior mitral leaflet during mitral valve repair.[19]

Other diagnostic modalities

Cinefluoroscopy. The exact visualization of mechanical prosthetic heart valve leaflet motion is best achieved by cinefluoroscopy.[15] It is a low-cost, noninvasive imaging technique, with limited radiation exposure that allows the correct evaluation of opening and closing angles and the motion of the base ring of the prosthetic heart valve and can add diagnostic value to echocardiography. It carries advantage over TEE for the visualization of leaflet motion in aortic prostheses, while the two modalities demonstrate comparable results in mitral prostheses.

Multidetector cardiac computed tomography. Multidetector cardiac computed tomography (MDCT) allows both precise estimation of the disc's mobility, as accurately as with fluoroscopy, and the differentiation between a thrombus and a pannus (although the exact cut-off values for this distinction have not been established yet), which is difficult with TEE mainly in the aortic position.[20] Biological leaflet thickening or restriction can also be detected. Furthermore, this modality has some limitations in patients with atrial fibrillation and those with dyspnoea and poor functional class because they are not able to lie in a supine position. In clinical practice, MDCT can be considered as a reliable investigation for further assessment of PVO, if the results of echocardiography are inconclusive, particularly for further evaluation of the obstructive abnormality (thrombus or pannus). If MDCT is performed, fluoroscopy can be omitted.

Cardiac magnetic resonance (MRI) has no role in PVO owing to valve-induced image artifacts.

Real-time three-dimensional TEE. Real-time three-dimensional TEE enables *en face* visualization of prosthetic valves and can be a promising diagnostic tool for the better detection and localization of thrombus or pannus overgrowth.[21]

Table 1. Recommendations in left-sided obstructive prosthetic valve thrombosis.

Guideline	Publication year	Main determinant	Treatment[a]
ESC[4]	2007	All patients	Surgery (I, C) (Fibrinolysis if surgery is contraindicated)
ACC/AHA[22]	2008	NYHA III−IV	Surgery (IIa, C) (fibrinolysis if surgery is contraindicated or unavailable)
		NYHA I−II, large thrombus burden	Surgery (IIa, C)
		NYHA I-II, small thrombus burden	Thrombolysis (IIb, B)
SHVD[23]	2005	Thrombus size >5 mm	Thrombolysis (regardless of NYHA class, unless contraindicated, presence of left atrial thrombus is contraindication)
ACCP[24]	2008	Thrombus burden <0.8 cm^2	Thrombolysis (II, C) (regardless of NYHA class)
		Thrombus burden >0.8 cm^2	Surgery (II, C) (thrombolysis if surgery is high risk or unavailable)

[a]Class and level of evidence are given. ACC/AHA, American College of Cadiology/American Heart Association; ACCP, American College of Chest Physicians; ESC, European Society of Cardiology; NYHA, New York Heart Association; SHVD, Society of Heart Valve Disease.

Treatment

The management of PVT depends on thrombus location and size, the patient's functional class, the risk of surgery or thrombolysis, and the clinician's experience.

Left-sided OPVT

Traditional therapy of left-sided OPVT is emergency surgery (valve replacement or thrombectomy), but thrombolysis has been proposed as an attractive first-line alternative.[1,22] The optimal management remains unclear because there is lack of randomized controlled trials to compare the two methods. Additionally the published guidelines (Table 1) differ significantly on whether surgery or thrombolysis should be the treatment of choice, as well as on which is the main determinant for the treatment (functional class, thrombus size, obstructive, or nonobstructive thrombosis).[4,22–24]

Surgery in left-sided OPVT. According to the 2007 European Society of Cardiology (ESC) and the 2008 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, surgery is the treatment of choice of left-sided OPVT.[4,22] The drawback of surgery is the high operative mortality (between 5% and 18%) which is largely related to clinical functional class, with New York Heart Association (NYHA) functional class at presentation to be a strong predictor of surgical mortality (4−7% in class I−III vs. 17.5−31.3% in class IV).[3,25] Thrombolysis followed by heparin infusion has been suggested as an alternative to surgery. It is associated with lower mortality rate but carries the risk of systemic embolism, bleeding, and rethrombosis.

Roudaut et al.[25], in the largest single-centre nonrandomized retrospective study, cited better early success rate and a significant lower incidence of complications for post-surgical than post-fibrinolytic therapy in left-sided OPVT. There was no difference between the two groups in terms of mortality (10%). However, complete haemodynamic success was significantly more frequent in the surgical group (81% vs. 70.9%) and embolic episodes were significantly more frequent in fibrinolysis group (1% vs. 0.7%), as were total complications (25% vs. 11.1%). The authors proposed thrombolysis as first-line therapy in cases of critically ill patients whose operative risk is high or if surgery cannot be performed urgently (rescue fibrinolysis).

Thrombolysis in left-sided OPVT. On the other hand, more recent studies show that fibrinolytic therapy can restore adequate function of the thrombosed prosthetic valve with high rates of success and lower mortality and complication rates than those reported by Roudaut et al.,[25] mainly in the post-TEE era. On this basis, thrombolysis is recommended as the first-line treatment for all patients with left-sided PVT by the Society for Heart Valve Disease (SHVD) guidelines and for patients with low thrombus burden (<0.8cm^2) regardless of functional class by the American College of Chest Physicians (ACCP) guidelines (Table 1).[23,24] The ACCP guidelines were based on PRO-TEE registry, which underscored the use of TEE for the proper selection of the patients for fibrinolytic therapy.[18] In a literature review, thrombolysis resulted in haemodynamic success rate of 64−89%.[18,26–28] The risk of systemic embolism was 5−19%, of major bleeding 5−8%, of recurrence as high as 15−31%, and the mortality rate 6−12.5%. Patients in NYHA IV class presented significantly less mortality post thrombolysis (7%) than did post surgery (17%), with the mortality rate of both therapies to be around 5% of patients in functional classes I−III. Fibrinolysis has a higher chance of being successful if the thrombus is younger than 14 days.[25] Chronic thrombosis resembles a pannus and clinically responds more poorly to thrombolysis. Therefore, a surgical approach might be considered in patients with chronic thrombosis. Thrombolysis does not preclude the patient from proceeding to surgery if there is no response. In the case of partial success, the patient might go to surgery in better haemodynamic condition with lower risk. Operation can be performed 24 hours

after the discontinuation of the infusion or 2 hours after fibrinolytic activity has been neutralized by protease inhibitors. Finally, the limited availability and high cost of surgery and the favourable clinical outcomes of fibrinolysis comparing with the surgical approach have made thrombolytic therapy the first-line treatment in many of the developing countries.

Thrombolytic agents. Currently used fibrinolytic agents are streptokinase, urokinase, and recombinant tissue-type plasminogen activator (rt-PA) in different regiments.[1] The conventional protocols have adapted from those used for the treatment of pulmonary thromboembolism: (a) streptokinase 250,000 IU over 30 min, 100,000 IU/h for up to 72−96 hours, (b) urokinase 4400 U/kg per hour for up to 12 hours; and (c) rt-PA 10−15 mg boluses following by 90−85 mg, respectively, in 90−180 min (total dose of 100 mg). Despite that accelerated protocols are attractive because they might achieve more rapid lysis of the thrombus, they increase the risk of serious bleeding and embolic events.[29] Keeping with this, recent data proposed that low dose of rt-PA (25 mg) and slow infusion (6 hours) resulted in mortality benefit derived from the lower rates of bleeding and systemic thromboembolism.[30] Serial TTE during the infusion allows the reassessment of thrombus resolution. Protocols should be stopped if stroke or bleeding occurs.

Right-sided PVT

Fibrinolysis is the first-line of therapy in right-sited PVT because there is no risk of cerebral embolism and the incidence of thromboembolism to the lungs is usually less serious than a cerebrovascular episode.[3,22] Lytic agents are also used as therapy for pulmonary embolism. Surgery can be considered for cases with a pannus, thrombolytic failure, and contraindication to thrombolysis, while there must be caution if there is patent foramen ovale or atrial septal defect.

Recurrent episodes of PVT

Fibrinolysis have been reported to be less efficacious for recurrent episodes of PVT than it is for the first episode, because it carries lower rate of complete haemodynamic response and higher risk of stroke and major bleeding. Recurrent episodes of PVT should probably be treated surgically.[31] Moreover, the surgical approach is the treatment of choice of patients with PVO associated with pannus formation. Strategies to prevent repeat PVT include the addition of low-dose aspirin, higher international normalized ratio, and, rarely, elective valve replacement by a bioprosthesis.[4]

NOPVT

The management options of NOPVT are based mainly on small samples observational studies. The treatment depends on thrombus size (small thrombus <5 mm in length, moderate thrombus between 5 and 10 mm in length), and the presence of embolism. For small asymptomatic thrombi (length <5 mm) the prognosis is favourable with medical therapy by optimization of anticoagulant treatment (short-term intravenous unfractionated heparin followed by warfarin adjustment and aspirin addition).[4,13,22,32] Conversely, if thrombus size is increased or is complicated by embolism, then thrombolytic therapy or surgery should be considered.[1,4,13] However, several studies have reported that fibrinolysis is safe and effective with low complications rate as first-line therapy in NOPVT, mainly if clot burden is greater than 5 mm.[18,23,27,33] The use of low-molecular-weight heparin in NOPVT is not clear yet.[34]

Conclusions

PVT can be an emergency condition with haemodynamic deterioration and high mortality. TEE plays an important role to the diagnosis and provides incremental information about the optimal treatment strategy. The remaining uncertainties in many aspects of the therapy of patients with PVT underline the need for prospective randomized controlled trials. The management depends on thrombus burden and location, NYHA functional class of the patient, the presence of embolism, the availability of surgery, the possible contraindications of each therapeutic option, and the clinician's experience. Ongoing progress in the design and performance of both mechanical and bioprosthetic heart valves, in combination with the use of new direct inhibitors of thrombin and factor Xa in the pharmacology field, may provide new perspectives for the future management of patients with PVT.[9]

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